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CHLORAMPHENICOL EXCRETION IN THE BILE

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It is well known that chloramphenicol is readily absorbed from the gastro-intestinal tract, and appears in the blood shortly after oral administration. Its presence in the bile after an interval of two hours has been reported by Gruhzit, Fisken, Reutner, and Martino (1949), by Glazko, Wolf, and Dill (1949), and by Long, Bliss, Schoenbach, Chandler, and Bryer (1950). In the following paper some details are given of its excretion in the bile.

METHODS

Absorption from the Portal Vein by the Liver.—After a 12-hr. fast, dogs of 8 and 13 kg. were given 80–100 mg. of chloramphenicol by mouth in a sufficient quantity of water. Half an hour later the abdomen was opened under chloralose anaesthesia, and blood samples were taken from the portal and hepatic veins.

Excretion in the Bile of Dogs.—After ligation and section of the common bile duct a biliary fistula was established. The general condition of the dogs remained good for a long period, for, by licking and swallowing some of the escaping bile, they obtained a a considerable quantity by mouth. The fistula was catheterized daily with a glass catheter to maintain patency. The bile flow was continuous, indicating bile of hepatic and not gall-bladder origin. About a month after operation the fistula was well organized and no bleeding followed catheterization.

In each experiment chloramphenicol was administered by stomach tube or oral syringe, and at the same time a rubber catheter was inserted into the fistula. Bile was flowing continuously, and blood and bile samples were collected at intervals after administration. The chloramphenicol estimations were made by the colorimetric method described by Bessman and Stevens (1950).

Excretion in Human Bile.—A dose of 250 mg. was given to a man weighing 46 kg. with a post-operative biliary fistula: blood and bile samples were collected after ½, 1, 2, 3, and 6 hr.

RESULTS

Samples of blood from the portal and hepatic veins of two dogs were analysed for their chloramphenicol content half an hour after administration of 80–100 mg. chloramphenicol by mouth. The results show that chloramphenicol is absorbed from the portal vein during its passage through the liver (Table I).

TABLE I

CONCENTRATION OF CHLORAMPHENICOL μG./ML. HALF AN HOUR AFTER ORAL ADMINISTRATION OF 80–100 MG.

	Portal Vein	Hepatic Vein
Dog, 8 kg.	12	4·0
„ 13 „	20	8·5

Two observations were made at intervals of ten days on the concentration of chloramphenicol in the blood and bile in each of two dogs, up to six hours after administration of 8 mg./kg. by mouth. As Fig. 1 shows, the blood concentration falls after

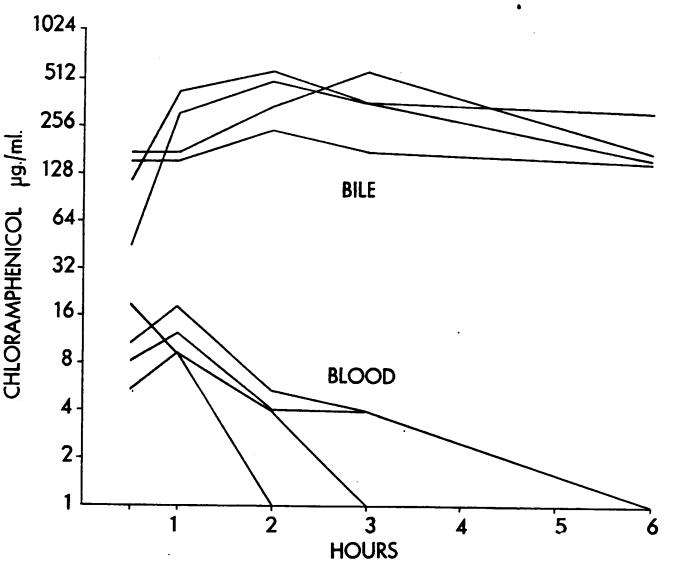

FIG. 1.—Blood and bile concentrations of chloramphenicol in two dogs after 8 mg./kg. by mouth. Two experiments at 10-day intervals on each dog.

one hour. Increasing the dose causes an almost proportionate increase in blood concentration. The concentration in the bile is 30–50 times that of the blood and, although it is highest between the second and third hours, it is still considerable six hours after administration. In one dog, given 24 mg./kg. by mouth, the blood and bile concentrations were measured up to 24 hours (Table II).

TABLE II

CONCENTRATION OF CHLORAMPHENICOL (μG./ML.) AFTER ORAL ADMINISTRATION

	Time Hrs.:	½	1	2	3	6	12	24
Dog 24 mg./kg.	Blood	—	10	—	22	13	6	2
	Bile	—	50	—	800	650	150	40
Man 5·4 mg./kg.	Blood	4	5	5	3	2	—	—
	Bile	3	8	12	32	1	—	—

At 12 hours the concentration in the bile had fallen considerably, and after 24 hours had reached approximately the same level as at one hour, one twentieth of its maximum.

A single observation in man (Table II) confirmed the impression, derived from these figures, that the concentration of chloramphenicol in the bile is well maintained for the first three hours even when the blood concentration is falling.

DISCUSSION

The steady and continuous flow of bile throughout these experiments suggested that the bile was of hepatic rather than gall-bladder origin. The high concentration of chloramphenicol in the bile is therefore due to the concentrating ability of the liver rather than the gall-bladder. The rapid rate of absorption of chloramphenicol by the liver is indicated by the gross difference in blood levels in the portal and hepatic veins.

In the absence of a biliary fistula the chloramphenicol excreted with the bile into the intestine is reabsorbed from the intestine and brought to the liver through the portal vein. Thereafter a part of it passes to the main circulation through the hepatic veins, and the remainder is again brought with the bile to the intestine. Thus, the reduced blood concentration observed in the second hour is not found under normal conditions, because of the continuous enterohepatic circulation of chloramphenicol. This enterohepatic circulation of the drug is important for two reasons—firstly, small doses of the drug remain in the systemic circulation for a longer time, and secondly the concentration in the biliary tract is higher.

This concentrating power of the human liver may be of practical importance in the treatment of cholangitis and cholecystitis. It may also apply in typhoid fever, for the typhoid bacillus frequently passes into the biliary system.

It should not be assumed that the chloramphenicol excreted in the bile is necessarily all active, for Chittenden, Sharp, Vonder Heide, Bratten, Glazko, and Stimpert (1949) demonstrated that only 15% of the chloramphenicol excreted in urine, as estimated colorimetrically, is in an active form. It is probable, therefore, that part of the chloramphenicol excreted with the bile is also inactive.

SUMMARY

1. Chloramphenicol administered by mouth is absorbed from the portal vein by the liver and excreted in considerably greater concentration in the bile.

2. It is reabsorbed from the intestine and carried to the liver again, undergoing an enterohepatic circulation similar to that of the bile salts.

3. The importance of this circulation is discussed.

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